Intraventricular Haemorrhage of the Newborn

Intraventricular haemorrhage occurs frequently in premature neonates. Large haemorrhages cause post-haemorrhagic ventricular dilatation, often requiring permanent CSF diversion. Elevated intracranial pressure, inflammatory cytokines and periventricular white matter distortion cause significant and permanent neurological disability. Progressive ventricular expansion is best controlled initially by regular aspiration through a ventricular access device. A combination of drainage, fibrinolysis and irrigation with artificial CSF also known as DRIFT, has been shown to improve neuro-developmental outcome at two years in a randomised study. It does not, however, reduce the need for ventriculoperitoneal shunt insertion. Future advances are likely to involve close collaboration between neonatologists and neurosurgeons.

Introduction

Intraventricular haemorrhage (IVH) remains an important problem in neonatal care and is characteristic of the premature infant. Improvements in neonatal care have led to a persistent decline in the mortality associated with prematurity. Currently, up to 90% of infants with birth weights between 500 and 1500g survive the neonatal period. Although advances in neonatal care have reduced the incidence of IVH in premature neonates, overall rates of IVH have generally been in the 20 to 25% range over the last two decades. IVH is more common at lower birth weights, and for infants weighing between 500 and 750g incidence is up to 45%. Post-haemorrhagic ventricular dilatation (PHVD) occurs in over half of those neonates with large bleeds. Up to 60% of these neonates become dependent on cerebrospinal fluid (CSF) shunts. Neurological outcome ultimately depends not only on the extent of periventricular leucomalacia related to injury to the oligodendrocyte precursors secondary to prematurity, but also on the management of PHVD and the complications related to CSF diversion, such as shunt malfunction and infection.

Pathophysiology

In prematurity, the source of the haemorrhage is the germinal matrix, located in the subependymal region. The germinal matrix gives origin to the cerebral neuroblasts and glia; it is highly cellular and gelatinous and is richly vascularised by capillaries that are poorly supported by muscle or collagen. It involutes in a rostro-caudal direction over the final 12 to 16 weeks of gestation. It is a fragile structure, and is prone to haemorrhage following abrupt changes in cerebral blood flow. In the premature neonate, such changes are often related to perinatal asphyxia and respiratory distress syndrome. IVH at term is rare and may be associated with trauma, vascular malformation or coagulopathy.

The occurrence of PHVD is directly related to the quantity of intraventricular blood. It may occur early as a result of aqueductal obstruction by haematoma, but more commonly it occurs as a result of a progressive obliterative arachnoiditis, involving the basal cisterns and the outlet foramina of the fourth ventricle. This disturbs the flow of CSF from the ventricles, where most is produced, to its absorption sites in the subarachnoid space; leading to a combination of communicating and obstructive hydrocephalus.

A number of cytokines, particularly transforming growth factor (TGF-β), have been associated with this process. TGF-β is a potent fibroblast activator, and upregulates genes expressing extracellular matrix proteins; these proteins are central to the development of obliterative arachnoiditis. TGF-β is not only secreted by astrocytes, meningeal cells and choroid plexus epithelial cells in response to inflammation, but is also released from alpha granules in the platelets within the IVH. In a clinical study, total TGF-β levels were higher in infants who developed PHVD, and were higher still in those who required insertion of a ventriculoperitoneal shunt. A rat pup model of PHVD has demonstrated increased TGF-β, laminin and fibronectin in the ependyma and subependymal tissue. However, intraventricular administration of decorin and oral administration of pirfenidone, both TGF-β antagonists, in the same rat pup model, did not lead to a reduction in ventricular size. Other cytokines, such as vascular endothelial growth factor (VEGF), are also likely to be involved.
The IVH itself is neurotoxic. Iron released from haem days after haemorrhage catalyses lipid peroxidation and exacerbates excitotoxicity. Non-protein bound iron levels in the CSF are markedly increased for several weeks after human neonatal IVH, enhancing the formation of reactive oxygen species at a time when antioxidant enzymes are not yet fully developed. In addition, the coagulation cascade releases thrombin, known to induce apoptosis in cultured neurons and astrocytes. The progressive accumulation of CSF in PHVD causes pressure on the peri-ventricular white matter, expanding the ventricles, and to a lesser extent, the compliant unfused skull, at the expense of brain volume. Neonatal intracranial pressure is normally under 6mmHg, but in the context of untreated PHVD it may rise to 10–15mmHg. It is the combination of inflammation, distortion, pressure and free radicals that causes significant injury to the poorly perfused neonatal white matter.

**Diagnosis and classification**

Both IVH and PHVD can be readily diagnosed on cranial ultrasound (Figure 1). The degree of IVH is traditionally defined according to the Papile classification. This recognises four kinds of IVH from mild to severe, as follows: grade I – subependymal haemorrhage; grade II – IVH; grade III – IVH with ventricular dilatation; grade IV – IVH with ventricular dilatation and parenchymal extension. Intraparenchymal involvement, however, is now no longer thought to represent merely an extension of the haemorrhage, but rather a venous haemorrhagic infarction, related to obstruction of the terminal vein at the ventricular angle by a large IVH. This reduces venous flow in the medullary and subependymal veins resulting in venous infarction (Figure 2).

The ventricular index is measured from the falx to the lateral wall of the body of the lateral ventricle; reference ranges for ventricular index according to gestational age are available. 4mm over the 97th centile is the ‘action line’ at which intervention is considered. Recognition of irregular or asymmetric ventricular expansion has led to definition of anterior horn width, measured diagonally (>4mm), third ventricular width, measured in the coronal plane (>3mm) and thalamo-occipital dimension, measured in the sagittal plane (>2mm) as new criteria for PHVD (Figure 3).

Untreated PHVD is associated with excessive head enlargement. Head circumference increases by about 1 mm daily between 26 and 32 weeks gestation; between 32 and 40 weeks it increases by 0.7 mm daily. An increase of 2mm per day is considered excessive, although this is difficult to detect with certainty over a single day – 4mm over two days, by the same observer, is more likely to be significant.

**Management of PHVD**

Repeated lumbar punctures (LP) are the simplest way to reduce ventricular size and intracranial pressure. Contrary to experience in adults, due to lower levels of intracranial pressure and open cranial sutures, coming after lumbar puncture is exceedingly rare in neonates. It is best to limit CSF removal to a sure and open cranial sutures, coning after direct ventricular puncture through the anterior fontanelle represents an alternative method of CSF aspiration; when repeated, however, needle track lesions through the cerebral hemisphere become evident. Repeated LPs or ventricular taps do not reduce the risk of forming campal diverticulum, and can be safely performed in neonates under 80mg. This is a temporary measure, and allows repeated drainage of CSF until the need for permanent CSF diversion can be established. An alternative, but less popular, temporary device is the ventriculostomy shunt.

A ventricular access device provides an easy and safe route for repeated aspiration of ventricular CSF with low infection rates. Insertion, through a frontal burr hole, requires a brief anaesthetic in a neurosurgical theatre, and can be safely performed in neonates under 80mg. This is a temporising measure, and allows repeated drainage of CSF until the need for permanent CSF diversion can be established. An alternative, but less popular, temporising device is the ventriculostomy shunt.

A ventricular access device remains controversial. In a retrospective study, early insertion, before crossing the 97th +4mm ventricular index line, showed lower rates of ventriculoperitoneal shunt. The Early versus Late Ventricular Intervention Study (ELVIS) is currently randomising between the two treatment thresholds, with death or shunt dependence and disability at two years the main treatment outcomes.

Drainage, irrigation and fibrinolysis therapy developed out of an attempt to reduce intracranial pressure and wash out the toxic cytokines from the ventricular system as early as possible. The procedure involves...
insertion of right frontal and left occipital catheters, with intraventricular injection of tissue plasminogen activator (tPA) that is insufficient to produce a systemic effect. Eight hours after tPA injection, irrigation with artificial CSF is commenced, at 20mL / hour, under intracranial pressure monitoring, aiming to maintain pressure below 7mmHg. The drainage fluid clears over about 72 hours, from a dark-coloured thick fluid to straw-coloured CSF.

A recent multi-centre randomised trial recruited 77 infants to DRIFT or standard treatment. Early results did not show any difference in the need for permanent CSF diversion in the DRIFT group.37 However, at two years, severe cognitive disability was significantly reduced in the DRIFT group.38 The median mental index in the DRIFT children was improved by more than 18 developmental points.39 This is the first intervention to demonstrate, within a randomised trial, an improved outcome in infants with PHVD.

The decision to insert a ventriculoperitoneal shunt should not be taken too early. Shunts in this population have a higher rate of failure and infection.6,7 It is ideal to wait at least until about term, when the body weight is at least 2kg, reducing risk of infection and skin ulceration over the shunt. CSF protein should be lower than 1.5g/L and repeated injection, irrigation with artificial CSF is commenced, at 20mL / hour, under intracranial pressure monitoring, aiming to maintain pressure below 7mmHg. The drainage fluid clears over about 72 hours, from a dark-coloured thick fluid to straw-coloured CSF.

The management of IVH and PHVD remains a significant challenge, and is likely, in the future, to incorporate a combination of mechanical and molecular therapeutic strategies. Close collaboration between neonatologists and neurosurgeons remains central to the development of a safe and effective treatment that maintains CSF circulation and optimises neurodevelopmental outcome.

REFERENCES